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Hypothalamic-Hypothyroidism Secondary to Sheehan's Syndrome

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THE RECENT AVAILABILITY of synthetic thyrotropin releasing hormone (TRH) for clinical testing has provided evidence that certain disorders affecting the hypothalamus or the hypothalamo-hypophyseal-portal system can lead to deficiencies in pituitary trophic hormone secretion. Indeed, some heretofore suspected primary pituitary lesions are now thought to be due to abnormalities in secretion of hypothalamic releasing factors.[1,2] Hypothalamic hypothyroidism, a condition characterized by low plasma thyroxine (T_4) and thyrotropin (TSH) concentrations, with normal TSH responsiveness to exogenous TRH administration, has been described recently in a variety of destructive lesions of the hypothalamus.[3-5] Also, patients with various congenital disorders, including nongoitrous cretinism[6] and idiopathic dwarfism[2] have been reported as having hypothalamic hypothyroidism as well.

This report describes the first known case of hypothalamic-hypothyroidism in a patient with Sheehan's syndrome, a disorder thought to be characterized primarily by hypopituitarism secondary to postpartum necrosis of the pituitary gland.

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Report of a Case

A 21-year-old woman was seen at the Clinical Research Center of the Los Angeles County-USC Medical Center with an 18-month history of progressive fatigue, anorexia, a 30-pound weight loss, loss of libido, amenorrhea, and loss of axillary and pubic hair. The symptoms had begun shortly after a full-term pregnancy had had to be terminated by cesarean section because of cephalopelvic disproportion. Two units of whole blood had been transfused at that time. There was failure of lactation portpartum.

On physical examination at the time of admission to hospital in 1969 the patient was thin and appeared to be chronically ill. Pulse rate was 72 beats per minute, respiratory rate 16 per minute, blood pressure 90/60 mm of mercury, and temperature 36.8°C (98.2°F). Pertinent physical findings included dry skin, delayed deep tendon reflexes, and absence of axillary and pubic hair. The visual fields were normal employing a red test object. Laboratory tests showed a hemoglobin of 10.3 grams per 100 ml, normal results of urinalysis, serum glucose of 72 mg per 100 ml, blood urea nitrogen (BUN) 9 mg per 100 ml, and normal serum electrolytes. Elevation of pituitary trophic hormones included assessment of immunoreactive growth hormone[7] reserve following insulin induced hypoglycemia, measurement of corticotropin (ACTH) reserve by detecting the change in 24-hour excretion of urinary ketogenic steroids[8] before and following the administration of methopyrapone, measurement of urinary bioassayable gonadotropins,[9] and assessment of immunoreactive plasma TSH.[10] Deficiencies in all of the pituitary trophic hormones were observed (Table 1). Other endocrine studies included measurement of serum thyroxine[11] and free thyroxine,[12] and the results were consistent with the diagnosis of hypothyroidism. A normal thyroidal response to exogenous TSH administration in the presence of a low plasma TSH level confirmed the presence of secondary hypothyroidism. Skull x-rays were normal including the sella turcica.

Therapy with thyroxine, 0.2 mg daily, and hydrocortisone, 20 mg daily, produced a satisfactory clinical response. The patient had a single menstrual period following three months of therapy and became pregnant again. Following a full-term pregnancy, a healthy child was delivered by cesarean section and the patient subsequently, without medical advice, discontinued taking her

TABLE 1.—*Endocrine Function Tests Following Pregnancies*

	Post First Pregnancy	*Post Second Pregnancy*	*Normal Values*
Plasma Growth Hormone			
Baseline	1.8 ng/ml	2.0 ng/ml	<10.0 ng/ml
Maximum*	4.0 ng/ml	<2.0 ng/ml	<10.0 ng/ml rise above baseline
Plasma Cortisol			
Baseline	N.D.†	<1.0 μg/100 ml	5-15 μg/100 ml
Maximum*	N.D.	2.0 μg/100 ml	10.0 μg/100 ml rise above baseline
Urinary 17-Ketogenic Steroids			
Baseline	4.0 mg/24 hrs	4.3 mg/24 hrs	6-16 mg/24 hrs
After Methopyrapone‡	6.6 mg/24 hrs	6.6 mg/24 hrs	3.0 mg/24 hrs × baseline
After ACTH§	N.D.	22.3 mg/24 hrs	3.0 mg/24 hrs × baseline
Urinary Gonadotropins	6-16, 6-16 mu/24 hrs	<6, 6-16 mu/24 hrs	16-50 mu/24 hrs
Serum TSH			
Baseline	1.2 μu/ml	1.1 μu/ml	<10.1 μu/ml
After TRH	N.D.	21.3 μu/ml	6.8-31.2 μu/ml
Serum Thyroxine¶	2.1 μg/100 ml	2.0 μg/100 ml	3.0-7.0 μg/100 ml
Free Thyroxine	0.9 mμg/100 ml	0.9 mμg/100 ml	1.0-2.3 mμg/100 ml
24-Hour Thyroidal RAIU			
Baseline	8 percent	8 percent	10-34 percent
After TSH‖	28 percent	19 percent	

*Following insulin-induced hypoglycemia.
†Indicates not done.
‡Methopyrapone, 750 mg orally every 4 hours for 12 doses.
§Synthetic ACTH, 25 units in 500 ml saline given I.V. over 8-hour period for 3 consecutive days.
¶Expressed as thyroxine iodine (performed by BioScience Laboratories, Van Nuys, California).
‖10 Units bovine TSH I.M. for 3 consecutive days.

medications. Several months later she was again admitted to the Clinical Research Center for recurrent symptoms of fatigue, weight loss and lack of libido. The patient did not lactate following the second pregnancy, and there was no resumption of menstrual periods.

Repeat hormonal determinations, which now included the plasma cortisol[13] response to insulin induced hypoglycemia, and the adrenal gland response to exogenously administered ACTH, indicated that there was persistence in deficiencies of anterior pituitary hormones (Table 1). Synthetic TRH, 500 μg, was administered intravenously in a single bolus and a normal TSH response to TRH stimulation was observed (Chart 1). A normal six-hour water deprivation study indicated adequate functional status of the posterior pituitary antidiuretic hormone production.

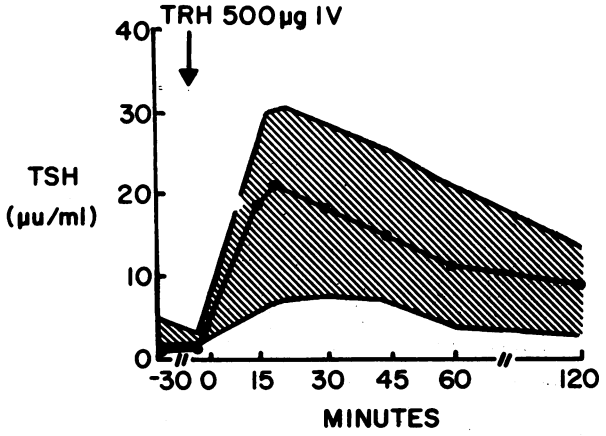

Chart 1.—TRH administration produced a normal plasma TSH response, depicted by the solid line connecting the dots. The shaded area represents the range of TSH responses to TRH observed in 23 normal subjects.

Discussion

The clinical findings and the results of the initial hormonal investigations in this patient were consistent with the diagnosis of Sheehan's syndrome with secondary hypothyroidism. However, the normal TSH response to exogenously administered TRH observed following the second pregnancy suggested a suprahypophyseal cause for the hypothyroidism. Since pituitary necrosis often characterizes the pathological findings in Sheehan's syndrome,[14] it would not be expected that the thyrotrophs would be capable of responding to exogenous TRH. However, it also has been shown that the primary lesion in this disorder may occasionally involve only the blood supply of the pituitary stalk.[15] Thus, diminished secretion of pituitary hormones could occur due to a deficiency in transport of hypophysiotrophic hormones. This type of lesion would be consistent with the observation of hypothalamic hypothyroidism in our patient. Indeed, recent evidence reported from our

laboratory suggests that a number of patients with Sheehan's syndrome may have impairment in endogenous TRH reserve or transport.[16] This does not appear to be a constant finding, however, since Fleischer and co-workers[17] have reported failure of synthetic TRH to induce a TSH rise in several patients with Sheehan's syndrome.

Another interesting feature of this patient's case was that she became pregnant following the diagnosis of Sheehan's syndrome. While pregnancy has been reported with this disease, it is uncommon and implies adequate secretion of pituitary gonadotropins.[18,19] The fact that pregnancy can occur with this disorder, however, serves to underscore the observation by Sheehan[20] that the syndrome can be atypical in its presentation and involve only several pituitary trophic hormones. Also, Sheehan[14] has provided evidence that the pituitary is occasionally capable of some repair following the original injury. It is possible, then, that in our patient either some gonadotropic function was spared following the first pregnancy, or was restored enough to allow another pregnancy to occur.

The most appealing hypothesis in this particular case, however, is that the patient's underlying lesion was suprahypophyseal, with impairment in synthesis, secretion, or transport of hypophysiotropic hormones. The most compelling evidence for this is that the patient was clinically and chemically hypothyroid, had low plasma TSH levels, and responded normally to TRH administration. It appears possible then that abnormalities in secretion or transport of the other hypothalamic releasing hormones may have been the cause of this patient's hypopituitarism. The recent availability of synthetic luteinizing releasing hormone (LRH) may offer an opportunity to further characterize the lesion leading to hypopituitarism in certain patients with Sheehan's syndrome.

Summary

A diagnosis of hypopituitarism was established in a 21-year-old woman 18 months after a full-term pregnancy which was complicated by postpartum hemorrhage. Shortly after hormonal replacement therapy was begun, the patient had a single menstrual period and became pregnant again. Following an uncomplicated pregnancy and delivery of a healthy child, she discontinued her medications, and signs of hypopituitarism again developed. Hormonal testing confirmed the presence of panhypopituitarism with hypothyroidism, yet administration of 500 μg of synthetic thyrotropin releasing hormone (TRH) produced a normal plasma thyrotropin (TSH) response. These data were consistent with the diagnosis of hypothalamic hypothyroidism, and suggested a suprahypophyseal cause for the panhypopituitarism in this patient, who may have had an atypical form of Sheehan's syndrome.

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